No. 2.—Dr. J. Burdon Sanderson's Reports of an experimental study of Infective Inflammations.

A.—Report of 1872.

Introduction.

When a living tissue is injured mechanically or chemically without being destroyed, it becomes the seat of a succession of changes which are the products of the disorder of the vital functions of the injured parts. These changes collectively receive the name Inflammation. The term comprehends, therefore, an assemblage of phenomena, held in relation with each other by the circumstance that they are all effects of the same injurious agency, and that they all form parts of one process, of which the various stages follow each other in more or less orderly succession.

Inflammation is the reaction of a living tissue against an injury.

It is not needful, in introducing the present inquiry, to describe the process of inflammation, for the question which concerns us has relation rather with the agency by which the phenomena are produced than with the manifestations of its action. It will be sufficient to remind the reader that the phenomena are of two kinds—those which depend on changes in the structural elements of the tissues, and those which have their seat in the blood-vessels; and that the latter, again, admit of a very obvious division, into those which concern the blood-vessels as muscular tubes (the contractile elements of which are under the immediate control of the vaso-motor nervous system), and those which relate to their function as mere conduits for the conveyance and distribution of blood.

If we compare these two orders of phenomena (the vascular and the textural effects of injury) with reference to their importance as characteristics of the process of inflammation, we shall assign the first place to the former, leaving the latter in subordinate and consequential relation to it; for although we know that a living part cannot be injured without the elements of its tissue undergoing those germinative changes of which the production and multiplication of young cells is the result, yet observation teaches us that this cell germination is never the first link in the chain of effects of which the reaction of a living tissue against an injury consists.

Of the two kinds of local changes of which inflammation consists (textural and vascular), the former are subordinate and subsequent to the latter.

The first local effect which an injury produces in a living part is vascular; it manifests itself as above indicated in two directions simultaneously. On the one hand, the state of contraction (or tonus) of the smallest arteries is altered or modified within and around the seat of injury in such a way as to determine increased supply of blood to the injured part; on the other, the walls of the capillaries undergo imperfectly understood changes, by virtue of which the liquor sanguinis (plasma) and corpuscles sweat or squeeze out into the lymphatic spaces in which the elements of the tissues lie.

This sweating out of the liquor sanguinis we call exudation, using the term in its original and etymological sense as distinguished from that which has been more recently given to it. Shortly after the introduction of the microscope as an instrument of pathological research, the microscopical study of the cellular products of inflammation so completely engrossed attention that by many writers the process or injury by which

The act of exudation is the link between the vascular and textural changes.

they were produced was altogether forgotten or left out of sight. So much so is this the case that in some of the best known text books of 20 years ago the word exudation is used as a name for certain sorts of liquids (purulent, tubercuIous, &c.), or for the cells which were then supposed to characterise them. On this account it is necessary to state that by exudation we mean the act of exudation and not the liquid resulting from that act.

The question of the relation between this act and the textural changes which are associated with it in the process of inflammation may, in accordance with what has preceded, be thus stated:—The tissue elements begin to germinate because they are stimulated, but the exciting action may be either identical with that by which the process is originated, or a secondary consequence of that action; in other words, the tissue may be acted on directly by the mechanical or chemical cause of the inflammation, or mediately by the flood of exuded liquor sanguinis with which it is irrigated. I have elsewhere stated* why it appears to me probable that in most inflammations the excitation of the tissues is indirect or secondary. This inference is mainly founded on the consideration that whereas we know of no instance of germination of tissue without exudation preceding or accompanying it, it can be proved by experiment that the introduction of exudation liquid into a healthy living part at once determines germinative changes. Admitting the facts, the proof is still incomplete, for it is not denied that there may be examples of textural germination occurring under the immediate influence of mechanical or chemical irritation without any antecedent exudation. If such instances exist they are at all events exceptional.

The notion that the liquid which is exuded in an injured part, as the immediate result of the injury, is itself the exciting agent by which the ulterior and more obvious changes are determined, appears at first sight to stand in very close relationship with the subject of the present inquiry; for if we say that all inflammatory liquids, even those of the most simple inflammations, are endowed with the property of irritating or exciting the elements of the tissues with which they come into contact, it seems very much the same as if we were to say that all inflammations are infective or contagious. If the word infective were to be understood as merely signifying the injurious action of a diseased product on healthy tissue, infectiveness would certainly be an attribute of every phlegmonous liquid. The difference in this respect between one inflammation and another would be merely a question of degree. But before accepting such a view of the subject, which, however logical it may appear, carries with it something which is opposed to experience, we must carefully consider whether the definition above referred to truly expresses the sense in which the word infective is intended to be used.

Definition of the term "infective" in its application to the products of inflammation:—Equivalent expressions in common use.

In the current language of the bedside it is usual to speak of inflammations being "healthy" or "unhealthy," and to distinguish between *pus bonum et laudabile* and other sorts of pus to which these favourable adjectives cannot be applied. The characters by which the good or bad quality of a purulent liquid, or the healthy or unhealthy conditions of a wound or granulating surface, may be distinguished are plainly set down in practical works, and thoroughly appreciated by every practical surgeon; and it is also well understood that unhealthy inflammations are not only distinguised by their objective characters, but also by the property which they have to produce general disorder of the health of the patient, and in their turn to be injuriously affected in their progress

* "The Process of Inflammation." Holmes' System of Surgery, 2nd Edition, vol. v., p. 786.

Inflammatory or traumatic fever.

by the disorder they have themselves produced. The constitutional state which is associated in this twofold way with inflammation as its product and its cause, exhibits variations which do not always correspond either with the extent or even with the intensity of the local process which it accompanies, and receives names which express that variation. It may be admitted that in all cases inflammation, if of considerable extent, is attended with fever; but there is a marked difference between the slight febrile disturbance which accompanies healthy suppuration and the degrees of general disorder which are expressed by such terms as "irritative fever," "pyæmia," or "septicæmia." These three, or the constitutional states that are associated with them, pass into each other by insensible gradations, but are separated from health by a line which has become much more easy to define practically at the bedside since the thermometer was introduced into every-day use as an aid to clinical observation.

To distinguish those inflammations which produce grave constitutional disturbance and secondary lesions, by an expressive word we call them *infecting*. In using the term we are guided by the same criterion as those on which the surgeon bases the practical distinctions above referred to. An inflammation which is more or less exactly limited in duration and extent by the limits of the injury which has caused it, may, with scientific precision, be designated a simple or normal inflammation. An inflammation which spreads and endures beyond the direct and primary operation of its cause, which induces similar inflammations in other parts, and disorders the vital functions of the whole body, has in it something beyond the effects of the injury, and may properly be termed *infective*. Thus infectiveness is marked by two sets of characteristics, one relating to what occurs at the original seat of inflammation, the other to the induced effects which manifest themselves elsewhere. Of the two groups of phenomena it is obvious that those which are removed from the seat of action claim most attention, for they afford evidence that material must have been discharged from the original focus, either by the absorbents or the veins, into the circulation. They consist partly in the springing up of new foci of inflammation along the course of the infected channels (the anatomical distribution of which secondary foci always distinctly indicates the source from which they have originated), partly in the occurrence of changes in the physical and organoleptic characters of the blood itself (not as yet investigated), of such a nature as to show that it is impregnated with the infective poison.

Previous observations showing that an inflammation may give rise to two infective processes, which, although associated in their origin, differ in their development. Of these, one is chronic, the other acute.

In the extended series of experiments made by the author in 1867 and 1868, one branch of the question of phlegmonous infection was worked out with some completeness. It was then found that when in the lower animals local inflammations are produced either in the skin or peritoneum by the introduction of irritant substances, two distinct sets of consequences manifest themselves, viz.: (1) a chronic disease exhibiting in all respects the anatomical characters of tuberculosis, and consisting essentially in the overgrowth of certain tissues then designated as lymphatic or adenoid, and shown to be in close relation with the lymphatic system; and (2) an acute disease presenting the leading features of pyæmia, attended with the formation of metastatic abscesses, and as a rule terminating fatally either very rapidly by intense peritonitis without any other appreciable lesion, or more slowly by the formation of infective abscesses and nodules, associated with inflammation not only of the peritoneum, but of other serous cavities.

These two morbid processes, the chronic and the acute, are both infective in the sense in which the word has been defined above, both

apparently spring from an infection derived from the same source (that is from the same primary infective focus), and progress in the same animal at the same time. These facts afford, however, no sufficient grounds for regarding the two processes as identical, for notwithstanding the closeness of their relation to each other, the differences cannot be overlooked.

Reasons for regarding these as essentially distinct.

The first reason for considering the two processes as different is to be found in the fact that, to a certain extent, either may be produced independently of the other at the will of the experimenter. In my former paper I showed that if an extremely small quantity of material from an enlarged and indurated gland of a tuberculized—*i.e.*, chronically infected—guinea-pig is injected into the pleura of another animal of the same species, it may happen that no appreciable constitutional disturbance is produced at the time, and so little local effect that if the animal is killed within two or three weeks after the inoculation no trace of lesion can be detected in the pleura or elsewhere. Eventually, however, the animal becomes tuberculous, the process beginning by the enlargement of the minute lymphatic masses of the pleural serosa.* More conclusive ground for regarding the two processes as pathologically different is to be found in the difference of their development. The acute affection attains its acme shortly after the infection, and associates itself in its progress with the primary inflammation produced at the seat of injury by the introduction of the infective agent. The chronic affection, when its phenomena are not complicated and modified by being mixed up with those of the acute, progresses so gradually that the appearance of the lesions seems to be preceded by a period of latency, during which the seed, so to speak, fails to germinate. Not that it can be supposed that the infective material is really latent, but that the earliest changes are so inconsiderable that they cannot be readily discovered.

The experimental results now to be reported relate entirely to acute, *i.e.*, pyæmic infection.

Modes of investigation.

General description of the results.

The investigations on which I have now to report enable me to state more clearly than I could before what is the true relation between these processes. The experiments differ from those referred to above in two important respects. In the first place, the material employed for exciting the primary inflammation was, as a rule, a product of an acute process; and secondly (what is of much greater importance), the quantity used for each insertion was ten or twenty times as large. Consequently in all cases the results obtained were, if the expression may be allowed, pyæmic rather than tuberculous. The animals were affected at once, suffered as a rule from well marked constitutional disturbance from the first, and died with or of intense inflammation in the serous cavities. The comparison of the lesions observed in these animals with those above referred to shows that in the acute cases, provided they live long enough, disseminated nodules are to be found in the serous membranes and in the substance of the abdominal and thoracic viscera, which soon assume the character of abscesses, and have the same, or at all events a very similar, distribution as the miliary nodules of the chronic process. They differ, however, alike in their prevalent characters and aspect, in their size, in their duration, and in the changes which they undergo.

Instead of slowly growing as if they were tumours, lasting for months in the vascular state, and eventually dying at their centres by a process of caseation as gradual as their growth, they enlarge rapidly, are soft from the first, and eventually assume the character of abscesses. We must, however, guard against the assumption that there is any original structural difference between the rapidly growing and suppurating

* Recent Researches on Artificial Tuberculosis. 1869. Pp. 1, 5, 7.

nodule and the slowly formed caseating granulation, for both originate by overgrowth of pre-existing elements—in other words by germination.* The difference between them is not one of origin or even of structure, but of duration and development; the one grows as if it were a part of the tissue from which it springs, until by the redundant multiplication of its closely packed elements, its central parts lose their blood supply; whereas the other becomes itself the seat of an acute inflammatory process. The conversion of a granulation into an abscess is I think perfectly parallel to the change which the granulating surface of a wound undergoes under the same conditions, *i.e.*, when it assumes the unhealthy character. Just as the newly formed vascular granulation softens and breaks down by a process of inflammation determined by the change which has taken place in the constitutional state of the patient, so we may readily understand that when the inoculated animal becomes the subject of infective fever, the interstitial indurations and granulations which would otherwise have retained their vascularity, firmness, and transparency for many months, may become acutely inflamed and become the seat of abscesses.† In like manner in phthisis pulmonalis in man the local condition of the diseased organ not merely determines the constitutional state, but is afterwards affected by it; so that the setting up of irritative fever from whatever cause determines the softening of parts which would otherwise have remained in a state of chronic induration.

A chronic, *i.e.*, tuberculous infective process becomes acute, *i.e.*, pyæmic under the influence of infective fever, adventitious tissues of all kinds being more prone to suppuration than normal ones.

In my introductory report on the intimate pathology of contagion, published in 1870, I brought together the general grounds which exist for the belief that the *materies morbi*, or contagium of contagious diseases, in general does not consist of substances chemically dissolved in the morbific liquid. The direct evidence in favour of the proposition was to be obtained from experiments which proved that in the case of some of the best known examples of infective action the toxic agent could be shown to be incapable of diffusion, and therefore in the strict sense insoluble. It was further argued, in the second part of the same paper, that if infective agents are particulate they are probably comprised in that group of bodies to which I then applied the term microzymes—recognizing their indentity with the zooglæa of Cohn, the micrococci of Hallier, and the various forms described by other authors under the terms *bacterium* and *vibrio*.

Existence of microzymes in the exudation-liquids of infective inflammations and in the blood of infected animals.

With reference to these organisms, two entirely new and most important facts have been demonstrated by the observations to be now recorded. It has been discovered (1) that in all acute infective inflammations microzymes abound in the exudation-liquids; and (2) that the same forms are also to be found in the blood of the infected animals, their presence being a constant accompaniment of all acute infective suppurations.

The more detailed statement of these facts will be found in the account to be immediately given of the experiments. It will, however, be convenient, in order to facilitate the understanding of that description, to explain here certain words which we have been in the habit of using to designate the varieties of form which are most frequently met with according to their grouping and mode of growth. These organisms present, in the exudation-liquids, characteristic appearances to which we apply various terms, such as colonies, bacterium filaments, dumb-bells and chains. The word *colony*, first introduced by Hallier, is used to

Explanation of certain words used in describing the microzymes of infective liquids.

* For reasons given in a former report I prefer the word germination to proliferation, used by many writers to express the same idea.

† It has not yet been proved experimentally that it is so.

designate groups of well defined contour, in which the individual microzymes are held together by their interstitial substance, which in this case forms a transparent matrix in which the rods and spheroids are embedded. A *bacterium filament* is simply a row of rods arranged end to end. A *dumb-bell* consists of two spheroids connected together by a bridge of envelope substance. A *chain* consists of a series of dumb-bells arranged end to end. Intermediate forms between dumb-bells and chains and rods or bacteria occur, which may be called *varicose rods.*

We have found it practically more convenient to use these common words* than to apply to the forms the specific designations used by morphologists, *e.g.*, *zooglæa* for colonies, *bacterium varicosum* for dumb-bells, *bacterium termo* for rods, &c.

As regards the morphological relation between these forms, I have little to add to what was stated in the last report. It is probable that they are organically continuous forms, but we are not in a position to state the precise relation in which they stand to each other.

It is, however, possible to divide them into two groups according to the circumstances under which they occur and thus to establish a classification, which, whatever may be its morphological significance, is of interest pathologically. Of these groups the rod is the type of one, the dumb-bell of another. In liquids in which the development of microzymes is going on with very great rapidity, as *e.g.*, in the exudation-liquid of intense infective peritonitis, single rods are found which are extremely minute, not larger than $\frac{1}{1000}$ millimeter in length. The less acute the process the larger the rods, and the more they are arranged in filaments end to end. In exudation-liquids, *e.g.*, in the liquid of a subcutaneous abscess, or of a peritonitis which has lasted for some weeks, there are scarcely any rods ; the prevalent forms are spheroids, dumb-bells, and chains.

The observations relating to exudation-liquids have entirely confirmed the conclusion arrived at in my former report with reference to the microzymes of ordinary drinking water, that they do not either originate from fungi or develop to them. On no single occasion has any form of mycelium been discovered in any of the innumerable infective liquids, charged with microzymes which have been examined.

Section I.—Previous Experiments on Acute Infection.

Before proceeding to bring under the notice of the reader the important results of the inquiries of the past year to which reference has just been made, I propose to give an account of some investigations made at former periods relating to the same subject.

Experiments in 1867.

In the year 1867 various experiments were made for the purpose of comparing the effect of inoculating various pyæmic or septicæmic liquids with those obtained by the insertion of minimal quantities of chronically indurated lymphatic glands or other products of chronic infection. I transcribe the notes of some of these experiments.

Aug. 23rd, 1867. Three guinea-pigs and a dog were inoculated with purulent liquid from the ankle joint of a patient affected with pyæmia. The patient, a man aged 28, was admitted into Middlesex Hospital under my care on the 20th of August, in a state of extreme typhoid depression. He complained of pains in all his joints and there was

* Since the above was written, Professor Cohn, of Breslau, has proposed an improved classification and nomenclature of bacteria, which will probably be in future generally used by pathologists. See his "Beiträge zur Biologie der Pflanzen," pp. 127–224.

effusion in the left knee and ankle. The day after his admission he had swelling and inflammation at the root of the nose which subsequently extending to the eyelids. The inflamed parts were soon covered with phlyctenæ, which rapidly suppurated and a fœtid discharge from the nostrils commenced. During the next day subcutaneous suppurations presented themselves in various parts, particularly in the left arm and right leg. In these situations the skin was swollen and livid, while numerous phlyctenoid pustules appeared in the neighbourhood. Death occurred during the following night. At the post-mortem examination the pustular eruption was found to consist of separate pustules and of confluent groups, both of which were more abundant on the face, and especially around the nose than elsewhere. There was an abscess in relation with the middle third of the left clavicle which extended outwards for two inches behind and below the bone ; no part of which, however, could be ascertained to be in a rough or denuded state. All of the subcutaneous abscesses, of which a considerable number were examined, were found to be lined by a thin but distinct membrane. Diffuse purulent infiltration was not found in any part of the body. The serous surface of the pericardium exhibited hæmorrhagic patches, and the blood contained in the cavities of the heart was uncoagulated ; it coagulated, however, when placed in a tube. Five or six nodules of grey induration were found under the pleura near the apex of the right lung, each being surrounded by apparently healthy lung tissue, and covered by healthy pleura. Other similar sub-pleural nodules were met with in the middle and lower lobes, but in the latter instead of being grey throughout they were blood-stained externally, so that the outer part resembled on section an apoplectic mass. In the left lung the nodules were smaller and less numerous. The abdominal organs exhibited no morbid appearances excepting those of hyperæmia. The blood was examined microscopically and found not to contain an excess of colourless blood corpuscles. In this case the pyæmic infection seemed to originate from the abscess near the left clavicle. The patient had complained of pain in this situation for ten days before any other symptoms presented themselves, during which time he was so free from constitutional ailment as to be able to attend to his occupation. He then began to suffer from pain in the joints, but had no serious symptoms until two days before his admission into the hospital. From the peculiar localization of the cutaneous cellulitis and pustular erruption, and the fœtid coryza, I at once inferred that the case was one of acute glanders ; but on careful inquiry found that the patient's mode of life was such as almost to preclude the possibility of this origin of the disease.

The first of the infected guinea-pigs died 15 days after inoculation. The inoculation was performed in the usual way, care being taken to use a very small quantity of liquid. The animal was found on the 7th of September with hurried and difficult breathing and loss of power of the hind legs. It was at once killed. The dissection is noted as follows :— Wound : a large abscess, of very irregular form, exists at the seat of inoculation, measuring at its greatest diameter no less than two inches ; it is lined by a well defined but thin membrane and contains caseous pus The scapular glands are not in the slightest degree enlarged and are perfectly transparent. The other sub-cutaneous glands are also healthy. Two of the mammæ are much swollen and are found when cut into to be infiltrated with pus which is partly creamy, partly caseous. Lungs healthy. The liver contains hard nodules as large as pin heads, which are scattered over the convex surface of the right and middle lobes. The spleen is much enlarged. Five or six nodules, varying in diameter from half a line to a line, project from its convex surface. Both the nodules

in the liver and those of the spleen, have the character of abscesses: they have firm capsules and contain pus which cannot be distinguished from that contained in those underneath the skin; they lie for the most part immediately underneath the serous membrane.—The second guinea-pig died 20 days after inoculation.* A large abscess exists at the seat of inoculation; a similar abscess is found over the gluteal muscles of the right side, containing creamy pus, enclosed in an extremely thin capsule, the surrounding tissue being slightly hyperæmic, but not indurated. There is a third abscess between the intercostal muscles and the pleura, which projects into the pleural cavity. The axillary tracheal and submaxillary glands are natural: the inguinal glands on the right side are slightly enlarged. On the surface of the lower lobe of the left lung there is a nodule of consolidation. On cutting into it, it is found to be intensely hyperæmic, and to have the characters of pneumonic consolidation. A layer of false membrane adheres to its pleural surface. Besides this there are grains of much firmer consistence which project above the pleura. Of these, four can be counted on the lower and one on the upper lobe, while in the right lung a group present themselves near the outer margin of the lower lobe. One of them, larger than the rest, contains creamy liquid in its centre. On the convex surface of the liver, nodules similar to those described in the other animal exist. The spleen is enlarged.—The dog, a small terrier weighing 8 lbs., died 49 days after inoculation, in a state of great exhaustion and emaciation. The inoculation wound could not be discovered, and the sub-cutaneous lymphatic glands were healthy. The lesions of the internal organs were as follows:—With the exception that minute hard nodules are disseminated over its convex surface, the liver appears to be healthy. The spleen is much enlarged, and contains groups of pale grey nodules in considerable numbers. The organ is adherent to the anterior wall of the abdominal cavity, as well as to the omentum and diaphragm, by softish false membranes, and the whole organ is covered with a layer of soft "lymph."—From one of the guinea-pigs two others were inoculated, both of which died within 48 hours after inoculation. Pus taken from the seat of inoculation was used to inoculate two others; one lived a month, the other 45 days. In both there were multiple abscesses under the skin; in the one which lived longest the right lung exhibited nodules and patches of lobular condensation with pleural adhesions. In the other the internal viscera were healthy.

On the 15th of December 1867 four guinea-pigs were inoculated with purulent liquid from the knee-joint of a man who had died of pyæmia. The patient, aged 42, was admitted into St. George's Hospital on the 20th of July with disease of the right astragalus and os calcis. Pyæmic symptoms supervened on the 3rd of December, and he died on the 14th. The liquid was taken and used about 20 hours after death. It was of a pale yellow colour, and opalescent appearance. Many of the pus corpuscles it contained were charged with fat granules. [Nothing was noted as to the presence of bacteria.] Of the four guinea-pigs, No. 1 died on the 21st day, the appearances being as follows:—An open wound exists at the seat of inoculation—A discharged abscess. Around the wound and extending from it towards the middle line, are several abscesses, some of which are confluent. The scapular gland of the side corresponding to the wound is enlarged and contains pus. The other sub-cutaneous glands and the internal organs are healthy. No. 2 died

* Whenever the present tense is employed the wording of the original notes is used. It is, however, abbreviated.

on the 22nd day; it was inoculated in two places. Both wounds are open and have indurated borders. Numerous small sub-cutaneous abscesses are scattered over both flanks in the neighbourhood of the wounds. The right middle lobe of the left lung contains in its depth a hard nodule about two lines in diameter. There are one or two sub-serous nodules in the spleen. The other organs are healthy. No. 3 died on the 26th day. The wound is open and a cord of induration extends from it for three-quarters of an inch to an abscess which is in immediate contact with the scapular gland, lying between it and the wound. The abscess measures five lines in diameter, and the gland, which is softened and contains creamy pus, is nearly as large. The other sub-cutaneous glands are healthy. [In this animal the internal organs were destroyed by its companions, so that they could not be examined.] No. 4 died on the 27th day. A very large abscess exists at the seat of inoculation, and a smaller one in its immediate neighbourhood. The scapular gland of the same side is enlarged and softened. The internal organs are found, on scrupulous examination, to be healthy. —On the 18th of November a guinea-pig was inoculated with pus from a pyæmic abscess in the posterior mediastinum of a patient who died in hospital on the previous day. The bodies of several dorsal vertebræ were diseased, and their excavated and roughened surfaces formed part of the wall of the abscess. There were pyæmic nodules in the lungs and kidneys. The animal was killed 32 days after inoculation. An abscess three or four lines in diameter, containing creamy pus enclosed in a membranous capsule, exists at the seat of inoculation. The capsule is firmly adherent to the skin and panniculus. The subcutaneous lymphatic glands are not enlarged, and the internal organs are healthy.

Experiments in 1871.

To these observations made in 1867–8 I append another of more recent date.* A girl aged 16 was admitted into the London Hospital on the 3rd July 1870, with strumous disease of the bones of the little finger and great toe. On the 12th of January 1871 the diseased organs were removed. The wound of the foot healed favourably, but that of the hand became unhealthy. Pyæmic symptoms (infective fever) appeared on the 26th. On the 7th of February an abscess was opened in the neighbourhood of the elbow joint. Pus was collected in calcined glass tubes which were immediately sealed. The same day the pus so collected was injected into the peritoneal cavities of several guinea-pigs according to the following method. In each case a sharpened cannula previously boiled is first introduced through the anterior abdominal wall into the peritoneum. A capillary tube open at one end and expanded at the other into a closed bulb having been prepared, the pus is discharged into a calcined cup of glass, like that used for holding vaccine in my former experiments. The open end of the capillary tube is then dipped into the pus, and filled by capillarity to a certain distance. [If desired, the quantity taken up can be easily determined by the balance.] The charged end is then passed by the cannula into the peritoneum, and the bulb slightly warmed, by which means the whole of the pus is discharged.—Nine weeks after inoculation two of these animals were dissected. Both exhibited the same appearances. The lesions observed (in No. 1) were as follows:—At the seat of puncture there is a slight induration. The inguinal glands are enlarged and softened on both sides; the scapular glands are also somewhat enlarged; but the other subcutaneous glands are normal. The inguinal glands, particularly on the right

* This experiment is briefly referred to in my report for 1871.

side, are surrounded by zones of intense injection, and there are numerous minute abscesses disseminated under the integument in their neighbourhood. Another group of abscesses surrounds the internal inguinal ring. The peritoneum is distended with sero-sanguineous liquid, in which are seen active bacteria of small size but very distinct form. The omentum is beset with minute nodules. The centrum tendineum of the diaphragm also exhibits a few nodules. The liver weighs 35 grammes: it is very pale and beset here and there with nodules, some of which are purulent. The spleen is enormously enlarged. [Condition of mesenteric glands not noted.] The pleuræ and the pericardium contain exudation liquid. Groups of opaque grey nodules are scattered throughout the lungs, both in the depth and at the surface.

Comparison of the lesions observed in animals inoculated with pyæmic products, with those produced when the material inoculated was derived from chronic secondary indurations.

The observations related in the preceding paragraphs show that although, as already stated, there is a close correspondence as regards the distribution of the infective nodules of the internal viscera between animals infected with pyæmic products and those inoculated with equally small quantities of the material derived from chronic secondary indurations, the contrast between the results is very marked. I will refer first to the lesions, and secondly to the development and mode of termination of the two processes. — *Subcutaneous lesions.* When an extremely small quantity of chronically enlarged lymphatic gland is inserted under the skin, in the manner described in my former paper, no abscess is produced either at the seat of inoculation or in any other situation. The wound to all appearance heals; but if it is carefully examined many weeks after, it is found, provided that the ingrafting has been successful, that a group of semi-transparent nodules exists under the skin, which represent the centre of infection. In the pyæmic cases there may also be induration of the same nature, but the nodules assume from the first the character of abscesses, and are accompanied by groups of smaller abscesses, disseminated in the neighbouring tissue. In a considerable proportion of the pyæmic animals these primary and secondary metastatic subcutaneous abscesses were the only lesions found, even though the dissections were made many weeks after inoculation. *Visceral lesions.* In chronically infected animals (using the term for animals infected by the insertion of minimal quantities of fresh induration material in the manner set down in the preceding paragraph) the visceral changes are much more uniform and characteristic. To judge of the difference between them and the corresponding pyæmic lesions, the several organs must be separately referred to. (1.) The chronically infected liver (*see* Eleventh Report, p. 110) does not usually present any morbid appearance to which the term "nodule" could be applied. The organ enlarges uniformly by the growth of a semi-transparent glistening interstitial substance, which, as it follows in its distribution the portal canals and occupies the spaces between acini and groups of acini, has an arborescent, not a nodular form, although the tracts of adventitious tissue exhibit nodular enlargement. Even when the change does not extend to the whole organ, but affects only a certain number of lobes, the newly formed tissue retains what descriptive pathological anatomists call the infiltrated as distinguished from the disseminated arrangement. In the acute affection the liver lesion is characterized by the presence of disseminated nodules, firm externally, purulent internally. (2.) The difference between the tuberculous lung and the pyæmic lung is perhaps not so obvious, but the characteristic appearance of the semi-transparent "iron grey nodules" (*loc. cit.*, p. 114), their uniform distribution throughout the parenchyma of the lungs, and the absence of concomitant pleuritic exudation or false membranes, are

facts which render the contrast between the two conditions sufficiently decided. (3.) Another very important distinction may be based on the condition of the lymphatic glands: in chronic (tuberculous) infection the internal lymphatic glands always become diseased tertiarily. They enlarge and pass into the state of chronic fibrous induration (*see loc. cit.*, p. 103), eventually becoming opaque and caseous. These changes may be well studied in the bronchial glands and particularly in those which receive their tributaries from the liver, in respect of both of which it may be observed that during the first two or three months after inoculation the glands remain unaffected. It is not until the pulmonary or hepatic disease has made some progress that the corresponding changes in the glands begin. In the acute affection it is entirely different. All the lymphatic glands which are in relation with the inflamed serous membranes become the seat of acute enlargement and softening. In tuberculosis they do not undergo this change, because the serous membranes are not inflamed.

Contrast between the two processes as regards development, progress, and mode of termination.

If we turn our attention from the lesions to the development and mode of termination of the two morbid processes, the contrast appears to be even greater. The most striking fact in this relation has been already referred to, viz., that when minimal quantities of induration material are used, the graft apparently lies hidden where it was inserted for many weeks, producing neither local inflammation nor fever (*loc. cit.*, p. 105), It is not till weeks have passed away that it begins to show its effect, first by the enlargement of the lymphatic glands in relation with the centre of infection, and then by the slowly progressing changes above referred to in the internal organs. The fatal result may, as my former observations showed, be postponed to an indefinite period, the animal living on in apparent health so long as there are sufficient of its organs unspoilt by the disease for the continuance of their functions. When it dies the result is usually determined by the setting up of an acute infective process, manifesting itself in serous inflammations, in the rapid softening of the indurated parts, and in the formation of vomicæ or abscess-like nodules in the diseased organs. Consequently, if we wish to study the chronic alterations of the internal viscera as they are, we must not wait till the animal dies, for by doing so we are almost sure to find them materially modified by the acute inflammatory softenings which precede the fatal issue. Just as in human pulmonary tuberculosis, so in the artificial disease, death is not caused by chronic induration, but by the acute infective inflammations which supervene upon them, or to which they furnish the occasion.

Section II.—Experiments on Acute Phlegmonous Infection, made during the year ending 31st March 1872.

First experiments as to conditions determining the presence of bacteria in peritoneal exudation-liquids.

I have already stated that in an experiment made in the spring of 1871 it was found that in animals infected by the introduction of a minimal quantity of pyæmic pus into the peritoneum, with all possible precautions against contamination of the infecting liquid by contact with other media, the peritoneal exudation-liquid was found to be charged with bacteria. This result suggested an important question. The presence of microzymes might be either a characteristic of the pyæmic process, or a mere result of the intensity of the peritonitis produced. To determine this, experiments were made during the following month (May 1871) which consisted in inducing intense peritonitis by the injection, not of exudation-liquids, but of chemical excitants, particularly dilute

ammonia and concentrated solution of iodine in hydriodic acid. As regards the ammonia, precautions were taken to guard against contamination by boiling and cooling the liquids as well as the implements to be used immediately before injection. In the case of the iodine solution this was, of course, unnecessary. In every instance it was found that the exudation liquids, collected from 24 to 48 hours after injection, were charged with bacteria; whence it appeared probable that the existence of these organisms was dependent, not on the nature of the exciting liquid by which the inflammation was induced, but on the intensity of the inflammation itself.

Division of the experiments into two series. Series I.—Experiments in which the exudation-liquids used were derived from infective inflammation of rapid progress.

After an interval of several months, occupied in other investigations, the inquiry was resumed. The experiments made may be divided into two series; in one those are comprised in which the liquids of acute infective inflammations were used, and consequently the results exhibited those characters of intensity and virulence which are expressed by the term septicæmia; in the others the results resembled those which have been already referred to in the preceding section, both as regards the methods and the phenomena induced. The important conclusions to which they have led will be stated after the facts themselves have been discussed. The following is a tabular summary of the experimental results of the first series :—

when introduced into the Peritoneum or into the Venous System.

Number.	Date.	Description of Exudation-Liquid used.	Designation of Test Animal.	Date of Dissection.	Duration of induced Inflammation.	Mode or Channel of introduction of infecting Liquid.	Quantity of infecting Liquid used. +	Result.
1	Jan. 9 -	Liquid obtained by puncture from the cavity of the uterus of a bitch affected with acute infective muco-enteritis and metritis. The animal was killed moribund, and immediately afterwards dissected. The liquid was charged with rods and dumb-bells.	Guinea pig 11	Jan. 10	c. 20 hours -	Peritoneum -	5 Div. (c. 6 ♏.)	Intense peritonitis; serous surfaces of stomach and intestines hyperæmic; sanguinolent exudation-liquid in peritoneal cavity. Exudation-liquid crowded with rods, along with a certain number of dumb-bells, chains, and colonies. Blood plasma particulate, the particles in tremulous movement.
2	Feb. 26	Purulent liquid from diffuse subcutaneous suppuration in groin of a rabbit, in which blood had been taken from the crural artery ten days before. The *plasma puris* is charged with rods and colonies of dumb-bells; the blood contains numerous minute rods, and here and there a dumb-bell. The animal was killed moribund, and immediately dissected.	Guinea pig 28 *a*	Feb. 27	12 hours- -	Do. -	3½ Div. (4 ♏.) -	Intense peritonitis; exudation-liquid milky, crowded with minute rods.
3	,, 26	Do. do. do. -	Guinea pig 28 *b*	Mar. 12	16 days - -	Do. -	Do. - -	Intense peritonitis, with false membranes on surfaces of viscera, and extensive adhesions; intense pleuritis; infective nodules (abscesses) in the abdominal viscera and underneath the peritoneum. Serous exudation-liquids abundant, crowded with rods, and containing other forms in small numbers; that of the pleura exhibits the particulate character. The purulent liquid of the pyæmic nodules in the liver contains rods in numbers, along with dumb-bells and chains. Blood tenacious; it contains numerous minute rods.

Tabular Summary of Observations relating to the action of the Exudation-Liquids of Acute Infective Inflammations—*continued.*

Number.	Date.	Description of Exudation-Liquid used.	Designation of Test Animal.	Date of Dissection.	Duration of induced Inflammation.	Mode or Channel of introduction of infecting Liquid.	Quantity of infecting Liquid used. +	Result.
4 and 5	Feb. 28	Peritoneal milky exudation-liquid of 28 *a*.	Guinea-pig 30 *a* and *b*	Feb. 28	10 hours -	Jugular vein -	5 Div. (6 ♏.) -	Both animals became collapsed soon after injection. Intense peritonitis; exudation-liquid crowded with rods of various sizes.
6	Mar. 12	Pleural exudation-liquid of 28 *b* -	Do. 39 *a*.	Mar. 26	16 days - -	Peritoneum -	2½ Div. (3 ♏.) -	Intense peritonitis and pleuritis, with false membranes covering surfaces of thoracic and abdominal viscera; consolidation of both lungs; pericarditis; pleural and peritoneal exudation-liquids crowded with bacteria.
7	„ 26	Pleural exudation-liquid of 39 *a* -	Dog I. XVI. *d*.	- -	- - -	Do. -	5 Div. (8 ♏.) -	This animal, after exhibiting for several hours the phenomena of acute infection (*i.e.*, rigors, followed by collapse with vomiting and purging), rapidly recovered.
8	„ 20	Purulent liquid from diffuse subcutaneous suppuration produced by injection of 3½ ♏. of dilute liquor ammoniæ under the skin of a guinea-pig. The liquid was charged with minute bacteria.	Guinea-pig 49 *a* and *b*	Mar. 20	6 hours - -	Do. -	3 Div. (3½ ♏.) -	Both animals became collapsed shortly after injection. Intense peritonitis; clear yellow viscid exudation-liquid, crowded with minute rods.
9	„ 20	Do. do. do. -	Do. 49 *c*	„ 21	24 hours -	Do. -	Do. - -	Post-mortem appearances the same.
10 and 11	„ 21	Peritoneal exudation-liquid of 49 *c*	50 *a* and *b*	„ 22	Do. - -	Do. -	Do. - -	Intense peritonitis; exudation-liquid viscid, and crowded with minute bacteria.
12	„ 23	Peritoneal exudation-liquid of 50 *a*	Dog XV. *d*.	„ 23	6 hours - -	Do. -	15 Div. (18 ♏.)	Death preceded by collapse, cramps, vomiting, and diarrhœa. Peritonitis and hæmorrhagic gastro-enteritis.
13 and 14	„ 16	Purulent liquid from the enlarged and softened mesenteric glands of 42 *a*. (See p. .)	Guinea-pig 44 *a* and *b*	„ 18	2 days - -	Do. -	4 Div. (5 ♏.) -	Intense peritonitis; purulent false membranes on the serous surfaces of the intestines and abdominal viscera; exudation-liquid viscid, swarming with minute short rods. Mesenteric glands enlarged and softened; one of them contains a large abscess, the purulent contents of which are charged with bacteria.

Number.	Date.	Description of Exudation-Liquid used.	Designation of Test Animal.	Date of Dissection.	Duration of induced Inflammation.	Mode or Channel of introduction of infecting Liquid.	Quantity of infecting Liquid used. +	Result.
15	Mar. 18	Purulent liquid from the enlarged and softened mesenteric glands of 44 *a*.	Guinea pig 46 *a*	Mar. 19	24 hours - -	Peritoneum -	4½ Div. (5½ m.) -	Intense peritonitis; exudation-liquid crowded with minute rods; other forms distinguishable with difficulty.
„	„ 18	Do. do. do. -	Do. 46 *b*	„ 29	11 days - -	Do. -	Do. -	Intense peritonitis with adhesions; infective nodules in omentum, mesenteric glands, and viscera; exudation-liquid viscid and crowded with rods, which also exist in number in the purulent contents of the nodules.
16, 17, & 18	„ 19	Peritoneal exudation-liquid of 46 *a*	Guinea pig 47 *a*, *b*, & *c*	„ 20	12 hours - -	Do. -	5 Div. (6 m.) -	All three animals became collapsed shortly after injection. General peritonitis; serous surfaces of intestines intensely injected; viscid exudation-liquid, crowded with rods.
19	„ 19	Do. do. do. -	Dog, VI. *d*.	„ 19	4 hours - -	Do. -	10 Div. (12 m.) -	The same symptoms during life and appearances after death as in No. 12 (see commentary).
20	„ 20	The same liquid kept since the preceding day in hermetically closed tubes.	Dog, VII. *d*.	„ 20	4½ hours - -	Do. -	Do. -	The same.
21	„ 20	Do. do. do. -	Cat, VIII. *e*	„ 21	5 hours - -	Do. -	Do. -	The same.
22	„ 20	Do. do. do. -	Cat, IX. *e*	„ 21	About 12 hours	Do. -	Do. -	The same.
23	„ 21	Do. do. do. -	Dog, X. *d*	„ 21	About 6½ hours	Do. -	6 Div. (7 m.) -	The same.
24	„ 21	Do. do. do. -	Dog, XI. *d*.	„ 22	About 12 hours	Jugular vein -	5 Div. (6 m.) -	The same. Symptoms extremely marked, and morbid changes excessive.
25	„ 21	The same liquid diluted with ¾ per cent. solution of chloride of sodium.	Cat, XII. *c*	„ 22	Do. - -	Peritoneum -	20 Div. (24 m.) -	The same.
26	, 21	Do. do. do. -	Cat, XIII. *c*	„ 24	About 3 days -	Jugular vein -	10 Div. (12 m.) -	The same.
27	„ 22	Blood of XI. *d*. charged with bacteria.	Dog, XIV. *a*	„ 22	19 hours - -	Peritoneum -	15 Div. (18 m.) -	The appearances on dissection indicate a peritonitis of extreme intensity. Surface of stomach and intestines covered with purulent false membranes; omentum intensely injected, and in parts in a state approaching gangrene; intense muco-enteritis of whole intestinal tract. Pleuritis, with sanguinolent exudation-liquid. Blood viscid, containing numerous minute bacteria.

Commentary on the Table.

In the first eight vertical columns the circumstances relating to the introduction of the exciting liquid are stated; in the last column the result as regards the conditions of the serous membranes and interna organs, and of the blood. The liquids used as excitants were in each case exudation-liquids; they were injected immediately after removal from the living animal. Of the 27 experiments, serous liquids were employed in 18; liquids of subcutaneous suppurations in four; liquid from softened infective nodules and lymphatic glands in three. In one, blood of the infected animal was used; and another, the content of an infectively inflamed uterus. All of these liquids were charged with bacteria at the moment that they were removed from the living animal. In the fourth column the test animals, or re-agents, are designated by numbers; the Arabic numerals relate to guinea-pigs, the Roman to cats or dogs. The fifth column gives the time after inoculation at which dissection was performed. In most cases the test animals were killed for the purpose when *in articulo*, in order that the blood and exudation-liquids might be examined in the recent state. In a few cases the dissections were made immediately after the animals had died naturally. From the sixth column it appears that in four cases the infecting liquid was injected into the jugular vein; in the rest into the peritoneum. The quantities used varied from 3 minims to 2 minims (consequently they were always incomparably greater than those employed in my experiments of 1867–68, which never exceeded a fifth of a minim).

Results.

Although the liquids were similar, all being products of rapidly progressing infective inflammations, the induced results were not all of equal intensity. Of the 27 animals used as re-agents, 20 died or became moribund within 24 hours, the mean duration of life after infection being about 13 hours. The others lived various periods from two days to 16 days. The protraction of the fatal result in these instances cannot be attributed to anything special in the particular experiments, for the table shows that in other animals injected at the same time and with the same material, no such postponement was observable. The fact illustrates a general principle which we shall see otherwise exemplified—that if an animal survives the first outburst of infective fever, it may be many days before it is exhausted by the subsequent secondary inflammations.

Of the 20 animals which died within 24 hours after infection, all excepting three (two guinea-pigs and a dog) received the excitant in the peritoneal cavity. In these three, in which the exudation-liquid was injected by the jugular vein, the signs of serous inflammation were quite as decided as in the others. All the 27 animals had intense peritonitis, and in the two guinea-pigs injected by the jugular vein both of which were moribund before the end of the day, it was just as intense as in any of the others. In the dog, in which the process was equally precipitate, it was specially noted that the changes observed on dissection happened to be more pronounced than in the animals of the same species which had received the same liquid directly into the abdominal cavity. Hence, although the local action of the exciting liquid cannot be regarded as insignificant, it is not the determining cause of the intensity of the peritonitis. This conclusion is confirmed by the observation that the pleura and pericardium were often as intensely affected by injections into the abdominal cavity as the peritoneum itself.

In cases which terminate rapidly peritonitis is pro-

From the fact that in all rapid cases of acute infection there is intense peritonitis, it might be surmised that the peritonitis is the immediate cause of death. Such an inference would be groundless and probably

erroneous. The symptoms which we recognise in the dog as those of intense infective fever, viz., collapse attended with vomiting and purging, manifested themselves so early in all the cases, and particularly in the animals which were injected by the jugular vein, that it would be difficult to regard them as secondary to the peritonitis. The rapidity and completeness of the recovery which takes place in some instances (*e.g.* in dog No. I.) after collapse of some duration affords additional ground for attributing collapse itself with its accompanying phenomena to the direct action of the infective agent.

probably not the immediate cause of death.

In all the very rapid cases the peritoneal liquid exhibited the same character. It was viscid, and coagulated imperfectly or not at all. It contained pus corpuscles, but they were relatively not numerous; the plasma (*liquor puris*) often exhibited a tremulous movement which under high powers is found to be due to the presence of minute rods. With lower powers particles cannot be distinguished; all that can be seen is the peculiar tremulous movement of the liquid, which, however, is sufficiently characteristic. In addition to this appearance, the liquid always contains other actively moving rod-like bodies, larger than the particles above mentioned, but still not greater than $\frac{1}{500}$ of a millimeter in length. In the most rapid cases dumb-bells and chains are mostly absent, but they soon appear if the peritonitis lasts long enough, or if the liquid is kept for a day in the warm chamber in a plugged eprouvette. In all the acutely infected animals to which the Table relates in which the blood was examined, it exhibited microscopical appearances which were characteristic and unequivocal. They were of two kinds, and corresponded to those already referred to as presenting themselves in the serous exudation-liquids. The blood plasma exhibited more or less distinctly tremulous movement of the particles above described, and contained short colourless corpuscles, often contained rods in their substance, and that the blood discs seemed to adhere to each other, the blood possessing a remarkable viscidity, the nature and significance of which will be a subject for future investigation.

Microscopical characters of the peritoneal exudation-liquid.

Microscopical characters of the blood.

General account of the symptoms and morbid appearances.

Symptoms.

The symptoms observed during life, and the changes found on dissection in acute phlegmonous infection, which terminate in less than 24 hours, differ considerably according to the animal used. In guinea-pigs collapse comes on very rapidly after injection, whether into the venous system or into the peritoneum. It is marked chiefly by loss of muscular power and diminution of temperature. After death there is intense peritonitis. In the dog or cat the phenomena are more marked. In some few cases the animal passes rapidly into the state of collapse, but more commonly an hour or two elapses before any very striking effect is observable. Among the earliest obvious phenomena are muscular twitchings and shiverings, which may come on during the second or third hour; but thermometrical measurements in the rectum show that the temperature rises from the first. The supervention of collapse is indicated by failure of muscular power. This is accompanied by retching and vomiting, which are soon followed by diarrhœa. The retching is associated with violent spasmodic muscular movements. As soon as the contents of the stomach have been expelled, a frothy greenish liquid of viscid consistence begins to be discharged. The diarrhœa is at first attended with tenesmus, but afterwards becomes colliquative. The alvine discharge is mucous, shreddy, and always more or less stained with altered blood. A few hours before death the temperature begins to sink, eventually falling below the normal; this depression begins soon after the accession of the more severe symptoms, so that the period at which the vomiting and purging come on with violence usually

Post mortem appearances.

corresponds to the acme of temperature. The most important of the changes observed after death are those which correspond with the symptoms. There is intense muco-enteritis of certain sections of the intestinal tract, the parts chiefly affected being the duodenum and rectum. The cases in which the alterations are most marked, are those in which, perhaps from great endurance on the part of the subject used, the toxic action, although equally intense, has been resisted a greater number of hours, so that it has had more time to develop itself. In such cases the whole tract may be inflamed, but in general the changes are limited as above stated. The mucous membrane of the duodenum is uniformly and intensely reddened, and its cavity distended with a mucous, more or less blood-stained, frothy liquid, in which float large flakes of exfoliated epithelium. The state of the rectum is similar, the staining of the mucous membrane is as deep and uniform, but the liquid is of a darker colour. The jejunum partakes more or less of the same conditions; but the ileum is always freer from change than any other part. Peyer's follicles are sometimes enlarged. The peritoneum is always hyperæmic in the most severe cases, and particularly the protracted ones, the hyperæmia is intense, and there are hæmorrhagic spots particularly on the omentum and mesentery. The characters of the exudation-liquid have been already referred to.

Comparison of the post-mortem appearances with those of putrid infection.

These symptoms and appearances closely correspond, if they are not absolutely identical, with those of septic infection in the dog, *i.e.*, with those which are produced by the injection of putrid animal liquids into the venous system. To illustrate this, I take the following account of the post-mortem appearances in this kind of poisoning from the well-known research of Bergmann on this subject.* After the injection of 4 to 7 cubic centimeters (60 to 100 minims) of putrid blood carefully filtered into the venous system of a large dog, the animal dies in from four to ten hours, the fatal issue being preceded by collapse, vomiting, and diarrhœa. On dissection, says Bergmann (p. 14), "the "most important post-mortem appearances are those found in the "intestine," consisting in "intense reddening and swelling of the "mucous membrane." In general the alteration "does not extend to "the whole intestine, but affects the pyloric end of the stomach, the "duodenum, the upper coils of the jejunum." . . . "The intestine is "filled with reddish thick mucous, which strikingly resembles the rose-"coloured rice water of the cholera stool. The further down in the "intestinal tract the liquid is examined the darker is its colour, until "in the large intestine it assumes a dull brownish red tinge which is "identical with that of the last alvine dejections. The quantity of "transudation-liquid in the intestine is very considerable. Even when "the extent of morbid alteration is greatest, it is mostly seen in the "upper part of the small intestine, colon, and rectum; the middle part "of the small intestine is either quite free or very slightly affected. ". . . . The greater the intensity and extent of this genuine gastro-"enteritis, the larger is the quantity in which shreds of separated "epithelium are mixed with the intestinal contents, and the more "abundant the excoriations and exfoliations of the mucous surface." . . . "In the worst cases an enteritis of equal intensity extends "the whole way from the cardia to the anal orifice. The croupous "diphtheric affection asserted by some observers to exist, I have not

* Dr. E. Bergmann, Das putride Gift und die putride Intoxication. Dorpat, 1868.

"observed. It appears to me that the yellowish shreds which separate "from the mucous surface are merely bits of shed epithelium."

The agreement of this description so far as relates to the mucous membrane of this intestine is complete. There is, however, one point of difference. Bergmann did not as a rule observe peritonitis in his animals. He records, indeed, that the mesenteric vessels were distended with blood, and that there were "sugillations" both in the mesentery and omentum; but it was only in two instances that he found the peritoneum generally inflamed. In these animals the exudation is described as being of a dirty brown colour, and very abundant; from which it seems reasonable to infer that in many other cases the condition was not observed, for it is scarcely probable that if the peritoneum was, as a rule, normal, it would be found in these two instances so intensely affected. It is much easier to believe that the very inconsiderable exudations which usually present themselves were overlooked.

In all other respects the differences are too inconsiderable to require special notice.

The inference above derived from the comparison of the phenomena of septic infection in the dog with those of acute phlegmonous infection, as to their close relation with each other, is confirmed by the following experiment, in which guinea-pigs were injected with exudation-liquids which had been kept for six days at the temperature of the body. It is seen that the results produced by such a liquid in the putrescent state, are not distinguishable from those which it produces when injected fresh in the same manner.

14th March.—Purulent liquid obtained from the spleen of a guinea-pig, which had been diluted with three-quarters per cent. solution of common salt, and kept at a temperature of 40° C. since the 8th, was injected into the peritoneal cavities of two other animals of the same species, the quantity used in each case being six minims. Both were moribund on the 16th. In the first there was intense peritonitis, and the peritoneum contained the usual viscid exudation-liquid. In addition to this there was œdema of the whole anterior half of the trunk. The blood vessels were dilated and distended with stagnant blood, over a region corresponding to that of the œdema, and extending from the middle line towards either flank. Beyond this region the vessels were remarkably empty. Not only the peritoneal liquid, but that of the subcutaneous œdema, was crowded with bacteria. The same forms were to be found in numbers in the blood, the plasma of which exhibited the particulate appearance already so often referred to. In the second animal, with the exception of the subcutaneous œdema, the appearances were similar. The blood and exudation-liquids exhibited the same characters.

Series II.—Experiments in which the liquids used were derived from chronic indurations in a state of suppurative disintegration.

I have now to refer to the second series of observations in which the infecting liquids were not products of virulent inflammation, such as those described in the last paragraph, but of more slowly progressing inflammatory processes, chiefly characterized by softening and unhealthy suppuration, either of infective nodules or of previously consolidated or infiltrated tissues. In the three series of experiments which will be given as examples of the rest, the original source of the infecting material was the diseased lungs of human beings or animals affected with chronic pulmonary tuberculosis in the stage of softening. The animals thus infected served in their turn as sources for the infection of others, the liquids used being derived from softened pyæmic nodules or lymphatic glands.

Dec. 22. A dog died in the Hospital for Animals of pulmonary phthisis of long duration. The condition of the left lung and pleura is noted as follows:—

There is a patch of consolidation about half an inch in diameter, over which the pleura is firmly adherent. Other similar nodules exist in other parts of the surface of the organ. On making sections it is found that each of these nodules is softened at its centre, and that around each, the lung substance is infiltrated as well as disseminated "with "grey and yellow tubercles." Of the remainder of the organ, the greater part is airless. The pleural cavity contains several ounces of clear liquid. Of the pleural exudation-liquid a few minims were injected into the peritoneal cavity of each of five guinea-pigs. Three others received a similar quantity of the purulent liquid from one of the softened nodules. The liquids were injected undiluted by means of a Pravas' syringe, the quantities used being relatively large. The animals were dissected respectively, 15, 23, 28, 34, 59, 66, 69, and 69 days after injection. The lesions were substantially the same in all, in every instance the serous membranes were inflamed and contained variable quantities of exudation-liquid charged with bacteria, in most cases there were extensive adhesions and false membranes; all of the organs contained infection nodules, which possessed the characters already described, being hard and firm externally with soft and purulent centres. The pus contained in them was always charged with microzymes both in the form of rods and in those of dumb-bells and chains. The latter forms prevailed most in those animals which had survived longest. In those liquids in which they were either absent or in relatively small numbers when the liquid was fresh, they multiplied rapidly when the liquid was placed for 24 hours in a warm chamber at the temperature of the body, while the rods seemed to undergo a corresponding diminution in numbers. This fact was observed very frequently in infective liquids so cultivated.

The contrast between the conditions observed in these experiments and those which characterise the chronic infection which is produced by the injection of minimal quantities of induration material is very striking. Here all of the lesions are the products of an acute process. This may be inferred from their characters, but we have a more positive ground for the conclusion that they are so in the fact that, in the animal which died at the end of a fortnight after injection, the infective abscesses in the internal organs were already fully developed, and that as regards the state of the serous cavities the appearances did not differ in any material respect from those which were observed in animals which survived 40, 50, or even 60 days. Clearly, if in the former case the mischief was done rapidly, we must believe that it was also done rapidly in the others, and that if we had had the opportunities of examining those animals which lived longest at the same early stage in the disease we should have found similar lesions. In either case we have to do with the products of a rapidly developed pyæmia, the lesions of which not only come into existence but attain their full development during the first few weeks after injection, the difference between the long cases and the others amounting to nothing more than that in the former the struggle was more protracted. Essentially the processes are the same. If one is acute, the other is.

The points of distinction referred to in the introductory section between acute and chronic infection (pyæmia and tuberculosis) are also well illustrated in the experiments now under consideration. Two perfectly conclusive facts may be referred to, in evidence that the process with which we are now concerned is not that which I described in my former papers. The one is that the lesions of the internal organs although

they accord with each other with the greatest exactitude as observed in the different animals of the same series, notwithstanding the differences of duration of the morbid processes, are entirely different from those described by me as characteristic of "artificial tuberculosis." The second is that, in the experiments now before us, the animals were the subjects of serous and other inflammations from the beginning, whereas in tuberculosis no lesion whatever is discoverable by microscopic examination until the fourth or fifth week after infection.

Dec. 30. Material derived from the lung of a patient who had died the day before of phthisis in the third stage, in the Hospital for Consumption, was injected into the peritoneum in three guinea-pigs, and under the skin in three others. The first three were dissected respectively, 29 and 44 days after inoculation, having either died of themselves or having been killed *in articulo*. The other two were killed, 24 and 68 days after injection. In the first three the lesions corresponded very closely with those already described. The pleura and peritoneum were inflamed and contained considerable quantities of exudation-liquid. The liver, spleen, and lungs contained pyæmic nodules, and there were similar nodules in the mesentery, omentum, and centrum tendineum of the diaphragm. One of the abscesses in the omentum was of very large size. The purulent liquid from the nodules contained rods and dumb-bells in great numbers; the latter were found as usual to have become much more numerous after the liquid had been kept for a day in the warm chamber. The same forms were seen in the pleural and peritoneal liquids. In all of these animals the blood was found to present the usual alterations. The plasma was particulate, the particles exhibiting the movement before described, and contained rods and dumb-bells. The other three experiments are of interest as showing how little the mode of insertion modifies the result as regards the internal lesions. They lived longer, but in other respects the morbid process was the same, and it is specially to be noted that the signs of pleural and peritoneal inflammations were quite as marked as in the others. Purulent liquid from one of the animals was injected im the usual way into the peritoneum of a healthy guinea-pig, which, on dissection three weeks later had peritonitis and infective nodules in the usual situations.

Feb. 27. A small female monkey died in the Hospital for Animals of pulmonary phthisis. The principal lesions were as follows:—In the thorax the morbid appearances are confined to the right side. The right pleura is everywhere adherent. The whole of the right lung, with the exception of the apex is either consolidated and airless, or beset with numerous disseminated nodules. These nodules are for the most part firm externally, but softened at their centres. Here and there, there are vomicæ. The peritoneum contains clear liquid, along the border of the colon there are several nodules varying in size from that of a pea to that of a hazel-nut. Of these the smaller are grey, the larger yellowish white on section. Similar but smaller nodules exist in the mesentery. In the liver there are numerous softened nodules as well as around the portal vessels. Purulent liquid from the pulmonary nodules containing microzymes of both forms was injected in the usual quantity into the peritoneal cavities of five guinea-pigs. The tests were dissected at periods varying from 30 to 43 days after infection. The post-mortem appearances, both as regards the serous membranes and the internal viscera, resembled in all respects those already described.

Conclusion.

Considering the complexity of the subject we have attempted to investigate, and the importance of the questions involved in it, it is

requisite to exercise extreme caution in drawing conclusions. There are, however, one or two propositions which may be stated with confidence as the results of our observations. It has been shown (1) that that combination of malignant fever with intense and destructive inflammations to which pathologists have rightly applied the term septicæmia, because it is known by experiment as well as by clinical observation to result from the existence in the blood of putrescent albuminous matter, may also be produced by the introduction, into the circulation or into the serous cavities, of small quantities of liquids derived directly from living tissues in certain states of inflammation; and that such states have the same distinctive characters as those which distinguish inflammation of septicæmic origin. (2) That pyæmia (the term being understood to denote a general febrile disorder of less virulence than that of septicæmia accompanied by numerous disseminated inflammations, characterised chiefly by their proneness to suppuration) is so closely related to septicæmia as regards its origin and essential nature that in these respects no line of distinction can be drawn between them; and that pyæmia, like septicæmia, may originate from a purely traumatic inflammation, independently of any infection with contagium derived from a previously existing pyæmic inflammation. (3) That both of these conditions are characterised by the existence of microzymes in the infected liquids; and that the relation of intensity between different cases of septicæmia and pyæmic infection is indicated by the number and character of these organisms; so that in the most intense processes, *i.e.*, those which exhibit the characters of septicæmia, the exudation-liquids and the blood are crowded with actively moving bacteria, while in the more chronic processes, the spheroidal and dumb-bell forms prevail, and the numbers of organisms found in the liquids are relatively inconsiderable.

Among the more important of the further considerations of inquiry which our researches suggest, are the relations between pyæmia and other states of disease, and particularly ordinary inflammation, and the relation of pyæmic or infective fever to the local inflammations with which it is associated.

The fact that ordinary traumatic inflammation may pass by an apparently gradual transition into a pyæmic or septic one, is evidence that the distinction is not always obvious, but does not prove that it is ill-defined or vague. For although it may be extremely difficult to say precisely when infective characters begin to manifest themselves, yet, if we are entitled to assume that the appearance of those characters is an evidence that an infective substance or contagium which was not there before, has come into existence in the blood or tissues, there must have been a moment at which that substance was introduced, and consequently a moment at which the process would have to be regarded no longer as the effect of the injury, but as the combined effect of the injury and the infection. In this way it is conceivable that the line between healthy and unhealthy inflammation may be in reality sharply defined, however faint and difficult to appreciate.

In our experiments of last year it was proved that, as a rule, the normal liquids of the animal body (blood, tissue, juice, &c.) do not contain microzymes either in germ or visible form. It was also proved that in common drinking water and in other watery liquids with which the body is constantly in contact, microzymes, although not distinguishable by the microscope, exist potentially, that is in germ. From these facts, taken in combination with the existence of similar organisms in infective exudation-liquids, the inference is very obvious that, inasmuch as these organisms cannot have originated from the normal tissues or juices, they must have been derived from the external moisture.

This inference would of course at once fall to the ground if it could be shown either that microzymes spring up of themselves, or that the forms which occur in the animal liquids are not specifically identical and organically continuous with those which exist in aqueous media outside. In the absence of any such proof, I am not aware of any objection to the assumption of their external origin, and am quite willing to admit it, provided that it is clearly understood that, even if the extrinsic origin of microzymes were proved, it would afford no ground for concluding that the origin of the contagium itself is also extrinsic. It does not at all follow because these organisms come in from outside that they bring contagium along with them ; for it may be readily admitted that they may serve as carriers of infection from diseased to healthy parts, or from diseased to healthy individuals, and yet be utterly devoid of any power of themselves originating the contagium they convey.

B.—Report of 1875.

In 1872 I had the honour of communicating to the Medical Department of the Privy Council a Report of investigations then made under their direction, on the subject of acute secondary inflammation in animals, the purpose of the inquiry being to throw light on the processes by which the infections which in man are associated with acute diseases of traumatic origin, are conveyed from diseased to healthy persons.

It having been shown by my own observations as well as by those of others, that in the various forms of secondary inflammation in animals, the exudation liquids of ordinary inflammations are always endowed with toxical properties which are not possessed by other animal fluids, and which manifest themselves either in the production of local inflammation in the living tissues with which such liquids are brought into contact, or in the production of acute general disorder consequent on their existence in the circulating blood or in the tissues, it became of importance that the nature of the toxical agent to which these effects are attributable, and the conditions of its action, should if possible be determined.

With this view a series of experiments was made in the Brown Institution at the period already referred to, of which some of the results were reported ; as however no opportunity then offered itself of making them public in the usual way, they were, with the permission of their Lordships, communicated to the Royal Medico-Chirurgical Society and published in the 56th volume of the Transactions of that body. They

were shortly afterwards translated into German and published in the *Wiener medicinische Jahrbücher*.

In the course of these experiments a new and most important fact came to light, namely, that in the transmission of infective inflammation in a series of animals, by inoculation from animal to animal, an *augmentation of infective activity* takes place, which is of such a nature that, whereas at the beginning of the series the effects produced by a given dose of infectious liquid are inconsiderable and transitory, a product is eventually obtained which possesses toxical powers of the most intense virulence. The experiments which led to the discovery of this fact were as follows:—

Experiment I.

On the 18th of March 1872, three and a half minims of dilute *liquor ammoniæ* (which had been previously boiled and cooled) were introduced into the peritonæal cavity of a guinea pig, the instruments used for the purpose being a cannula which had just been subjected to prolonged boiling, and a freshly made glass pipette. On the day following, the animal was killed, and the exudation liquid contained in the peritonæal cavity was immediately injected into the peritonæal cavities of two other guinea pigs, of which one became collapsed soon after the injection, and survived only six hours; the other was killed about 24 hours afterwards. In both animals there was intense peritonitis. In the second guinea pig (which was killed) the fluid exudation was clear and viscid and of a yellow colour; it was crowded with minute organisms.

On the following day three and a half minims of this fluid were injected into the peritonæal cavities of two other guinea pigs, neither of which survived more than 24 hours. Exudation liquid was collected from one of them in a glass tube just drawn out and cooled, and immediately sealed up hermetically. Of this product 18 minims were on the 23rd, *i.e.*, two days after, injected into the peritonæum of a moderate sized dog. Death occurred in six hours. Shortly after the injection the animal became affected with tenesmus, vomiting, and diarrhœa, which speedily subsided into fatal collapse.

Experiment II.

Five minims of liquid derived from an infectively inflamed lymphatic gland of a guinea pig, were injected into the peritonæal cavity of two others on the 16th of March.

In both animals the injection resulted in intense peritonitis, with purulent false membranes on the serous surfaces of the viscera. In one of them, which survived two days, the mesenteric glands were enlarged and softened. On the 18th, five minims of purulent liquid derived from one of these softened mesenteric glands, and charged with organisms, were introduced into the peritonæum of another guinea pig. In this animal the peritonitis was again very intense, and yielded an exudation fluid, which was injected into three others, each receiving six minims, all of which became collapsed shortly after the injection. After death the peritonæal cavity, of which the surface was intensely injected, was found to contain viscid exudation fluid crowded with organisms. The extreme activity of the virulent liquid was further tested by injection to carnivora, namely to four dogs and two cats; of the former, three received

from seven to twelve minims each in the peritonæum, the fourth by injection into a vein. Death occurred at various periods between four and twelve hours, and was preceded by collapse ushered in by vomiting, tenesmus, and diarrhœa. In the two cats the phenomena were essentially the same, the duration being five hours in the one case and two in the other.

From the above experiments, which with others were tabulated in the Report of 1872, it was ascertained that when in a series of rodent animals and particularly guinea pigs, inflammation of the peritonæum is communicated from one to another, by the injection into the peritonæal cavity of each in its turn, of exudation liquid derived from its predecessor, the process thus transmitted appears to gain in intensity by transmission, so that sooner or later a product is obtained which, when tested by injection into the peritonæum of a carnivorous animal, is found to possess an extreme degree of virulence.

In order to determine under what circumstances this intensification occurs, and to obtain more precise information as to the phenomena during life, and the pathological appearances after death, with which it is associated, I have more recently thought it necessary to make the following experiments, which have also been carried out at the Brown Institution :—

Experiment III.

The form of the experiment is shown in the diagram.

Primary peritonitis was induced on the 3rd of February 1875 by the subcutaneous injection of four cubic centims. of a mixture of nine parts of distilled water with one part of liquor ammoniæ. The liquid was boiled and cooled. Twenty-four hours afterwards a large quantity of subcutaneous exudation liquid was obtained from the moribund animals, of which 1·62 cubic-centims. were injected to the next in the series (No. 2). From No. 2, which died during the following night, peritonæal exudation liquid was injected into the peritonæum of No. 3, the dose being reduced to 0·486 c. c. (= six divisions of the Pravaz syringe used). Similarly No. 4 was infected from No. 3, and No. 5 from No. 4. In each of the three last-mentioned animals the process was extremely rapid, so that it was difficult or impossible to make useful comparisons of their conditions during life; in No. 5, however, it was apparent, that although the dose of infecting liquid was reduced to four divisions, the induced process had reached an extreme degree of intensity, death occurring in four and a half hours after injection. This being the case, we injected on the afternoon of February 8th five divisions of peritonæal liquid of No. 5 into No. 6. On the following morning it was found that the cannula had failed to enter the peritonæum. We therefore withdrew some of the subcutaneous exudation thus produced, and injected it immediately into the peritonæum

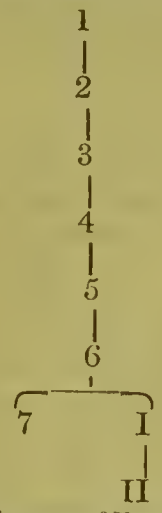


Diagram of Experiment III. The Arabic numerals indicate guinea pigs; the Roman, dogs.

of the same animal. By this expedient we obtained in No. 6, after 10 hours, a sufficient quantity of viscid peritonæal exudation fluid, which we at once recognised as having in all respects the same characters as the extremely virulent fluid with which we had experimented in 1872.

Having thus good reason to believe that we had accomplished our object, we injected two divisions of this liquid to another guinea pig (No. 7), and eight divisions to a dog (No. I.). The former died during the following night, yielding an exudation liquid which was exactly the counterpart of that by which it was produced; the latter survived for nine hours. From its peritonæum, liquid was obtained immediately after death, and at once injected in similar dose into the peritonæum of another dog (No. II.), which died in seven hours.

It was thus conclusively shown that it is possible to proceed from an inflammation of purely non-infective origin, to the artificial induction of a process of the most intense virulence. The phenomena observed in the several animals used were as follows:—

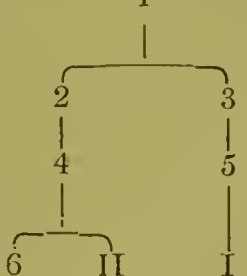
1. In the guinea pigs 3, 4, and 5 the exudation liquids were for the most part muddy, and showed a mere trace of sanguinolent staining. On microscopical examination they were found to contain no blood disks, but numerous pus corpuscles. In No. 3 these corpuscles floated freely and singly in the liquid, but in 4 and 5, where they were in greater numbers, were aggregated in clumps. In all the liquids microphytes were abundant, but they presented different characters; in three they were mostly rods of various but usually considerable length; in 4 and 5, rod-forms also occurred in considerable numbers, but they were shorter, (commonly about twice as long as broad), and more minute. In addition to these, the liquids of 4 and 5 contained countless myriads of spheroids (micrococci) which were either free or in masses. It is by these masses of living spheroids that the pus corpuscles are held together so as to form the clumps already mentioned. In all the animals it was observed that the exudation liquid in the pleura—the inflammation of which was of course secondary, *i.e.*, produced by infection from the peritonæum—presented in each case characters which corresponded with those observed in the peritonæum itself.

2. In No. 6, as has been already stated, the point of the cannula unintentionally failed to enter the peritonæum, in consequence of which the injected fluid was diffused in the tissues of the abdominal wall. Sixteen hours after, a swelling existed at the seat of puncture, from which a liquid was withdrawn, and at once transferred to the peritonæal cavity. The resulting peritonæal exudation collected after 10 hours, differed from those previously described in being perfectly colourless, milky, and viscid; it was found to contain numerous pus corpuscles, which, as in the other exudations, were collected together in clumps, of which the interstitial material consisted of masses of spheroidal organisms. The liquid in which the clumps floated was also crowded with shining spheroids, some of which were isolated, others in dumb-bells or chains. Rod-like bacteria were entirely absent. Every pus corpuscle was itself crowded with spheroids embedded in the substance of its protoplasm. The colourless and viscid exudation liquid which was obtained from the guinea pig No. 7, which was injected with the liquid just described, resembled it in every respect, excepting that in addition to the microscopical clumps, the field was scattered with larger fleecy masses of micrococci also containing pus corpuscles. This liquid was slightly alkaline, and left on evaporation at 100° C. 5·01 per cent. of solid residue. The specific gravity was 1019·3.

3. In order to test the activity of the exudation liquid of No. 6, a black and tan terrier, weighing about 8 lbs., received in the peritonæum, one and a half divisions of it mixed with an equal quantity of half per cent. saline solution. The animal shivered violently an hour after the injection, and had diarrhœa and vomiting soon after. The enteric symptoms attained their greatest violence about four hours after injection, at which time the animal appeared to suffer much from tenesmus; the *sphincter ani* was relaxed, and there were frequent discharges of bloodstained mucus. Death happened eight hours after injection. The maximum of pyrexia was attained during the fourth hour; the highest temperature observed was 41°·2 C.(106°·2 F.), the previous normal being 38°·6 (101°·5 F.). On dissection, the peritonæal cavity was found to contain a muddy sanguinolent liquid; on microscopical examination it was seen to be crowded with large pus corpuscles, all of which were charged with micrococci. Both the pleural and peritonæal surfaces exhibited hæmorrhagic spots, but the pleura in this case contained no exudation. The dog No. II., weighing 9 lbs., received 3·9 cub. centims. of peritonæal liquid from No. I. Two hours after injection there were severe rigors, but scarcely any rise of temperature. In two hours more, the animal was moribund, its temperature having sunk to 35°·3 C. On dissection the peritonæal cavity was found to contain a considerable quantity of blood-coloured viscid fluid; the omentum and mesentery were beset with hæmorrhagic spots. The mucous membrane of the stomach and of the whole intestinal tract was intensely congested, being of a dark crimson colour throughout. Microscopical examination showed the exudation liquid to contain numerous pus corpuscles, all of which were charged with micrococci. Similar organisms also existed free, but not in such crowds as in the colourless viscid exudations of guinea pigs. Notwithstanding the intensely sanguinolent colour of the liquid, it contained scarcely any blood disks.

Experiment IV.

Primary inflammation was produced as in the former case, by the injection into the subcutaneous cellular tissue, of eight-tenths of a cubic centimeter of dilute ammonia. Thirty hours afterwards an abundant exudation had taken place under the skin in the neighbourhood of the seat of injection; there was also exudation fluid in the pleuræ. Of the former, seven divisions were injected into the peritonæal cavity of guinea pig No. 2, and of the latter a similar quantity to No. 3. No. 3 died in four hours; the exudation liquid served for the injection of No. 5. This animal yielded a characteristic colourless viscid liquid which was at once injected into the peritonæum of dog No. I. The dog died in six hours, with intense symptoms. At the same time that No. 5 was infected from 3, II 4 was infected from 2, affording in its turn liquid for the infection of two other animals, a dog (No. II.) and a guinea pig (No. 6.)



In these eight animals, the symptoms and pathological appearances were as follows:

The animal primarily affected survived injection 30 hours. The subcutaneous liquid was slightly alkaline: its specific gravity was 1017·4 and it left on evaporation at 100° C. 5·3 per cent. of solid residue. It contained very few blood disks, and relatively few pus cor-

puscles, but it was crowded with rod-like filaments of various lengths, along with spheroids, chains, and dumb-bells, in considerable numbers, and a few crystals of ammonio-magnesic phosphate. The exudation liquid collected from the pleuræ contained no filamentous organisms, (bacteria proper) but innumerable spheroids, and a few short chains and dumb-bells: there were also a few pus cells, in all of which the cell substance was beset with spheroids.

Guinea pig No. 3, which was injected at 12 o'clock with the pleural liquid just described, died about 4 the same afternoon. The peritonæal exudation was pale-coloured and viscid. It contained flakes or shreds, visible to the naked eye, and was crowded with free spheroids, dumb-bells, and chains, amongst which no rods or filaments could be distinguished. It also contained pus corpuscles, some of which were isolated, others in clumps. In these clumps, as well as in the larger shreds already referred to, the corpuscles were held together by a mass of spheroidal particles.

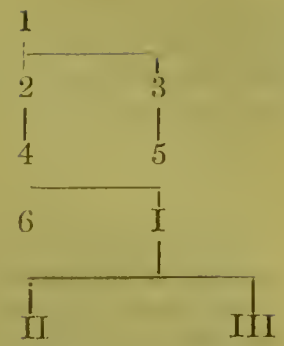
Guinea pig No. 5, which was injected at 5 o'clock with four divisions of the peritonæal liquid of No. 3, was already moribund at 9 in the evening. On the following morning the exudation liquid contained in its peritonæal cavity was collected. It was pale, viscid, and crowded with organisms, which corresponded in character to those found in the exudation liquid of No. 3. It was used to inject dog No. I.

Dog No. I., weighing about forty pounds, received fifteen divisions of the liquid of No. 5. The injection was made at 11.30 a.m., and death occurred at 5 p.m., the symptoms being those already described as characteristic of intense infection. On opening the abdominal cavity after death, the peritonæum was found to be intensely hyperæmic, the mesenteric veins being distended with blood, and the surface of the mesentery as well as that of the omentum scattered with numerous hæmorrhagic spots. The mucous surface of the stomach and small intestines was so intensely congested, that it was of a uniform dark red colour throughout. It was covered with a layer of bloodstained mucus, which material constituted the only contents of the stomach and intestine. The peritonæal exudation liquid contained 15·08 per cent. of solids, its specific gravity being 1041. It was slightly alkaline, and did not coagulate spontaneously even when placed in the warm chamber at 32° C.; on the addition of serum, however, it became flaky. Notwithstanding its intensely sanguinolent colour, it was found on microscopical examination to contain scarcely a single blood disk; in microscopical preparations, crystals of hæmoglobin were found in abundance near the edges of the cover glass; a few drops of the liquid allowed to evaporate in a watch glass also crystallized readily. Pus corpuscles and endothelial elements, either isolated or in clumps, existed in great numbers; the former contained innumerable spheroids embedded in their substance; the liquid was charged with the usual forms, particularly spheroids and dumb-bells of extreme minuteness.

The dog No. II (weight 10 pounds), which was smaller than the one last referred to, and received a similar dose of exudation from the peritonæum of guinea pig No. 4, exhibited similar symptoms, but recovered. The guinea pig injected at the same time (Febr. 20), and with the same liquid, survived seven hours. The colourless viscid exudation contained in its peritonæum having been collected in a glass tube and sealed hermetically, 10 divisions of it were subsequently (Febr. 23) employed to infect dog No. II a second time, the animal having completely recovered. His temperature rose in consequence only eight-tenths of a degree in three hours, and then declined. He recovered without further symptoms.

Experiment V.

On the 22nd February 1875, eight divisions of boiled and cooled solution of ammonia, containing before boiling one part in ten of liquor ammoniæ, were injected subcutaneously to a guinea pig (No. 1). The animal survived 21 hours, and afforded material for the infection of two others, one of which (No. 3) received exudation liquid collected from the peritonæal cavity; the other (No. 2) the liquid effused subcutaneously in the neighbourhood of the puncture. From the latter the guinea pig No 4 was infected, and from that the guinea pig No. 6 and the dog No. I. which finally served to infect two others; from the former, liquid was collected for the injection of No. 5.



In guinea pig No. 1 the quantity of subcutaneous liquid was relatively very small, and differed from those previously used in the small number of pus corpuscles it contained. The peritonæal and pleural liquids exhibited the usual appearances, and contained rods, spheroids, and dumb-bells in great numbers. In No. 2 the period of survival could not be determined, but was probably about eight hours. The viscid exudation liquid from the peritonæum contained, along with the usual anatomical elements, spheroids, dumb-bells, and short chains, which were either isolated or in small masses. None of the liquids coagulated. In guinea pigs Nos. 3 and 6 the peritonæal liquids presented the usual characters, the period of survival being in each case about seven hours. In both the blood was carefully examined, and found to contain spheroids similar to those of the exudation liquids.

The dog, No. I., weighing 15 lbs., which received in its peritonæum 3·9 cubic centims. of the same liquid which was used for the infection of No. 6, survived seven hours, exhibiting the same symptoms as in the other cases. The appearances observed on dissection, were also similar to those already fully described in Exp. IV., but by no means so intense. Both the peritonæal liquid and that obtained from the secondarily inflamed pleuræ were crowded with the organisms usually observed, the presence of which could also be detected in the blood.

From this animal two others were infected, but by different channels. Dog No. II., weighing about 6 lbs., received in the peritonæum four divisions (*i.e.* $\frac{1}{10}$ of the previous dose) of peritonæal exudation from No. I., and died in 14 hours, with the usual symptoms and post-mortem appearances. In dog No. III. 5 cubic centimeters of peritonæal exudation, previously filtered through paper, were injected on the 1st of March into the circulation by the tibial vein. The immediate effect produced by the injection was very inconsiderable, the maximum rise of temperature amounting only to 1°·6 C., *i.e.*, not more than is often produced by the injection of a similar quantity of distilled water; but the following morning the animal refused food and was apparently in pain. On the 3rd (the day after) he was still suffering; when an attempt was made to examine him, he struggled so violently, that it was found impossible to observe his temperature. Next morning he was killed, and the body immediately afterwards dissected.

On removing the integument covering the thorax, a quantity of pale yellowish exudation was found infiltrating the tissue in the neighbourhood of the articulations of the fourth and fifth ribs with their cartilages, and extending to the intermuscular spaces to a short distance. In pursuing the examination, similar cellular infiltrations were found in

other parts, particularly subcutaneous tissue about the left elbow joint, and around the left tarsus. The internal viscera were apparently healthy. The pleural and peritonæal cavities were sparingly studded with hæmorrhagic spots, and contained small quantities of liquid which on microscopical examination, was found to contain the usual organisms.

Conclusions.

From the preceding experiments we learn that whenever an inflammation is produced in a guinea pig, of such a nature as to result in the exudation of liquid, either in the cellular tissues or into a serous cavity, that exudation liquid possesses an infective property which, for the purpose of distinguishing it from the properties of other morbid contagia as well as from that which manifests itself in the production of fever, may be designated *phlogogenic*, the property in question consisting in this, that if such a liquid is injected into a second animal of the same species, *it produces an inflammation which is similar in character to that of which it is itself the product.* Inflammations so produced we may conveniently term "transmitted inflammations," reserving the expression "secondary inflammations" for those which originate in the same organism at a distance from any traumatic (primary) inflammation, by self infection.

We have seen it to be the result of observation that the intensity of any transmitted inflammation is dependent on the intensity of the inflammatory process by which it was produced, or, in other words, that those transmitted inflammations are most intense which are begotten of the most intense antecedents. We have also seen that if a process of inflammation is transmitted in a series of animals from one to another in such a way that each is infected by the introduction into its body of exudation liquid derived from its predecessor, the transmitted process become on the whole more intense towards ths end of the series. But it is not true, as I was at first inclined to suppose, that this increase of intensity by transmission progresses in a gradual or regular manner. I have learnt this by direct observation. All the experiments, and particularly the third and fourth, which were expressly contrived for the purpose of showing such gradual intensification, distinctly indicate that the augmentation does not take place by successive steps but *per saltum.*

How this happens may, I think, be readily understood if it be borne in mind, that the intensity of a transmitted inflammation is determined not merely by that of its immediate antecedent, or, in other words, by the virulence of the transmitted liquid, but also by the condition of the individual animal which is the subject of it. If the augmentation were a gradual one, we should express the whole truth in comparing it to a process of cultivation, that is, in supposing that the phlogogenic agent *itself*, by passing from the body of one animal to that of another, undergoes a gradual development of its infective power, in a manner comparable to that in which we imagine a plant to be modified gradually by being planted in a soil different from that to which it is naturally habituated. The fact that this is not the case, but that in a series of transmissions the intensification of virulence appears, as it were, *per saltum*, can have no other explanation than the one already suggested, namely, that the conditions belonging to the infected individual are no less efficacious than those which belong to the material transmitted.

This being admitted, there are two such conditions as regards the guinea pig to which importance is to be attributed, viz., susceptibility and endurance. As regards susceptibility, it is so nearly equal in all

cases, that its influence becomes inappreciable ; for our observations show distinctly, that inflammations which are the products of not more than two or three transmissions, may in some cases present the characteristics of extreme intensity. But in respect of enduranee there is no such uniformity ; all guinea pigs are in the highest degree prone to infection, but all are by no means equally capable of resisting its effects. Many succumb before the process has had time to culminate, and for this reason yield products of an inferior degree of virulence. The most active products are yielded by animals which have *longest* resisted the *most intense* process ; so that if I were asked by what method a phlogogenic virus of great activity could with most certainty be obtained, I should say, by first injecting a produet of not less than two transmissions to a sufficient number of guinea pigs, and then selecting as a source of virus that which held out the longest.

The fact that in the guinea pig the transmitted inflammatory process may arrive *per saltum* at its highest degree of intensity, even when the infecting liquid is the product of only two transmissions, renders that animal unfit to serve as a eriterion, or qnantitative test, of any excepting the lower degrees of virulencc, just as a spring balance which is stretched nearly to its utmost when loaded to a few ounces, would be of no use in estimating the weight of an object weighing as many pounds. It is for this reason that we have recourse to a standard of less susceptibility.

Such a test we have in the dog, for the organism of the dog appears to be as averse from infection as that of the guinea pig is prone to it. In this respect its condition is probably very near that of man when in health, for which reason the dog is a better standard of eomparison than the rodent. Both, however, have their value, for in certain states of health the suseeptibility of the human organism, normally intermediate between that of the rodent and that of the carnivora, appears to be enormously increased.

In the dog, as I have ascertained by a sufficient number of experiments not here stated, the injection of a cubic centimeter of primary exudation liquid, *i.e.*, of liquid produeed directly by the injection of ammonia or of solution of iodine into the peritonæum, produces no appreciable effect—not because a liquid of this kind is free from infectiveness, for as we have already seen, it acts powerfully on the guinea pig, but because the living tissues of the dog have resistance enough to eounteract its influenee. It is not until we deal with exudation products of the highest degree of virulence, that we obtain those decisive effects of whieh I have given instances in the preceding paragraphs.

In employing the dog as a test of the infeetive activity of an exudation liqnid, whether derived from another animal of the same species or from a rodent, it is important not merely to determine by experiment the smallest dose of the agent or material to be investigated, which is capable of producing fatal infection, but to endeavonr to measure the intensity of the action in each case, by the pathological appearances found after death and by the symptoms during life. As regards the latter, the means which is of most use in enabling us to judge of the intensity of an infective process, is the observation of the changes of bodily temperature which follow infection. Of these, three principal varieties have presented themselves in the course of our experiments. In what may be called the normal case, in which a liquid of moderate intensity is used, the injection is followed, after a very short period of latency, by violent rigors attended by rapid rise of temperature, during and after which the animal has more or less of vomiting and tenesmus, and discharges mucous or sangninolent evacuations. Secondly, we have cases

representing the smallest appreciable degree of infective action, in which the rise of temperature, inconsiderable as it is, is the only sign of constitutional disturbance; and lastly, those in which the elevation of temperature is also slight, but for a very different reason. Of these last we have a good example in Experiment IV. In this animal the rigors commenced within two hours after the injection, but the bodily temperature, which had previously maintained itself a fraction of a degree above the normal, fell rapidly after the close of the third hour, until the animal died collapsed.

These phenomena are readily enough understood if attention is paid to the relation between the temperature changes, and the condition of the animal. What may be called the normal effect of the introduction of an infective agent into the organism, is to produce rigors with coincident and consequent pyrexia, attaining its maximum in three or four hours and then subsiding. But this standard may be departed from either in the direction of excess or in that of defect. In the former case, where the absence of pyrexia is due to excess of infective action, it denotes not that the agency which in the less severe cases produces pyrexia is absent or even in abeyance, but that its influence is counteracted by others, and particularly by those which tend to general weakening of systemic life and diminished circulation.

Notwithstanding the apparently intimate relation between the elevation of temperature and infective action of the kind we are now engaged in studying, it is not by any means to be taken for granted that this elevation results directly from the introduction of the infective agent into the circulating blood. There is, on the contrary, reason for believing that here, as in the case of the specific infections, the pyrexia is rather a secondary result of processes having their seat in the inflamed part than of a direct absorption into the blood of phlogogenic virus; for we have repeatedly observed, that even when considerable doses of virulent liquids are injected directly into the blood-stream, the resulting fever is often very inconsiderable. Hence we conclude, that although in all infective inflammations the presence of a fever-producing agent is plainly indicated, it would be a mistake to regard the phlogogenic and the pyrogenic actions as identical in their nature.

In conclusion I would refer to the differences which present themselves between infective liquids of different intensities. These differences are so characteristic, that the practised observer has no difficulty in recognizing a highly infective product by its physical and microscopical characters, even if unacquainted with the pathological condition under which it was produced. The highly infective serous exudation products of guinea pigs, have always a high specific gravity, fail to coagulate, and possess a viscidity so peculiar that it alone would serve as a characteristic. They are further distinguished by the presence of the spheroids and dumb-bells so often referred to, either isolated in the liquid, collected in colonies or cloud-like masses, or embedded in the cell substance of pus corpuscles. In the dog the same characters present themselves, with this important difference, which I am quite unable to account for,—that, as the reader must have noticed, the liquids are almost always more or less blood-coloured, whereas in the guinea pig they are always colourless. The staining is very often so intense that it might be supposed to arise from extravasation. There is, however, no difficulty in proving the contrary, for on microscopical examination it is found to contain absolutely no blood disks, and when examined by the naked eye with transmitted light (as, for instance, when enclosed between two glass plates held between the eye and a window) it is seen

to be transparent. The blood-colouring matter, therefore which is present, is not in its natural condition, but in a state similar to that in which it exists in blood which has been several times frozen and thawed, a fact of which proof can be readily obtained by slowly evaporating a small quantity of the exudation liquid in a watch glass. As evaporation proceeds, hæmoglobin crystallizes.

In conclusion, I think it desirable to repeat what I have often had occasion to insist on elsewhere, that the presence of characteristic organic forms in infective liquids, affords *in itself* no conclusive evidence that these bodies are themselves the cause of the infectiveness. If we inferred from the constancy of their characteristics and from their invariable presence, that they are the *agents* which produce the pathological results, we might be as seriously in error as those are who maintain, in the face of all the investigations relating to the subject made during the last few years, that they are without pathological significance. There is nothing in nature, and particularly in organic nature, without significance, nor ought it in the slightest degree to diminish the interest which we take in any phenomenon, that we are unacquainted with its relation to the other phenomena with which we find it associated. If these infinitely minute organisms are present in every intensely infective inflammation, we may be quite sure that they stand in important relation to the morbid process.